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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/575,522

04/12/2006

Nafizal Hossain

06275-503US1

3659

26164 7590 05/16/2007

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EXAMINER

O DELL, DAVID K

ART UNIT

PAPER NUMBER

1609

MAIL DATE

DELIVERY MODE

05/16/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,522	HOSSAIN, NAFIZAL	
	Examiner	Art Unit	
	David K. O'Dell, Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 12-18 is/are pending in the application.
- 4a) Of the above claim(s) 8, 10 and 12-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12 April 2006 & 9 March 2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-10, 12-18 are pending in the current application.
2. This is a National Stage of PCT/SE2004/001476, filed October 14, 2004, which claims priority to Swedish Application Serial No. 0302755-4, filed October 17, 2003.

Applicant's Response to Restriction/Election

3. Applicant's election without traverse of Group I in the reply filed on April 30, 2007 is acknowledged.

Group I, Claims 1-7, 9 drawn to compounds and compositions possessing a spirocyclic benzofuran-cyclohexyl core, where in applicant's Markush structure of Formula I X is a bond, Y is O, Z is CH₂, q is 1, R₂=R₄=R₅=R₆=R₇=H shown as structure I in Figure 1.

This requirement is made final. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*; *In re Brouwer* and 35 U.S.C. §103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended

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during prosecution to require the limitations of the product claims. Applicants are reminded of propriety of process of use claims in consideration of the "reach-through" format, which is drawn to mechanistic, receptor binding or enzymatic functionality. Reach-through claims are considered lacking of descriptive and enabling support from the specification. Thus, rejoinable process of use claims are those with particular disease named with efficacy support from the specification for treating the particular disease. This application contains claims drawn to an invention nonelected without traverse in the reply filed on April 30, 2007. A complete reply to this rejection must include cancellation of nonelected claims or other appropriate action

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

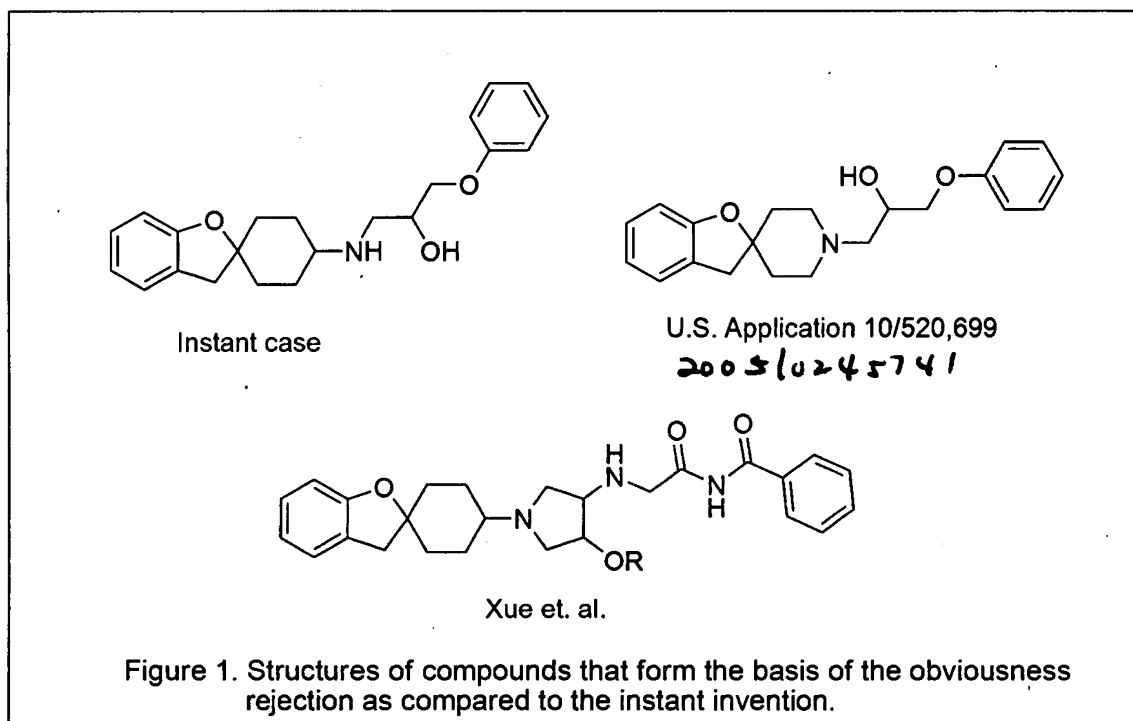
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-7, 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et. al. U.S. Pre-Grant Publication 2006/0252751 and Hossain, Nafizal; Ivanova, Svetlana; Mensonides-Harsema, Marguerite U.S. Pre-Grant Publication US 2005/0245741 A1. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

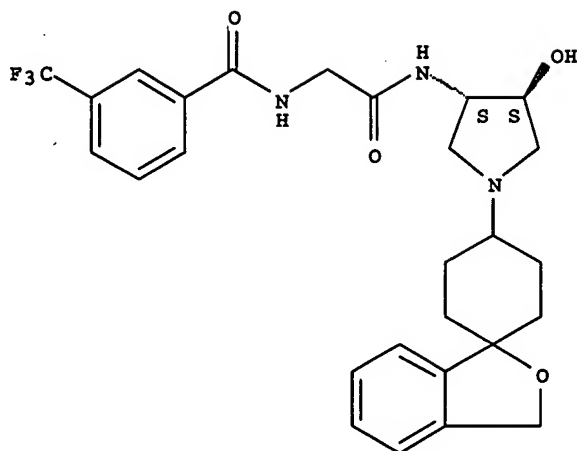
Xue et. al. teaches spiro[benzofuran-2,1'-cyclohexan]-4'-amines that are chemokine antagonists. Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite teach spiro[benzofuran-2,4'-piperidines bearing a 1-phenoxy-3-propan-2-ol substituent on the piperidinyll nitrogen atom. This relationship is illustrated graphically in Figure 1.



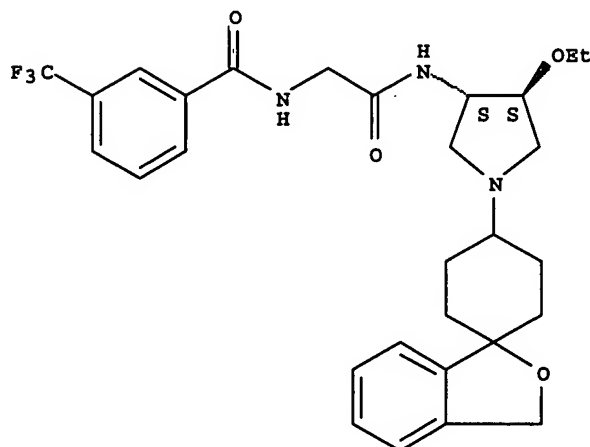
Some of the compounds disclosed by Xue are show below:

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Registry #: 709019-00-1

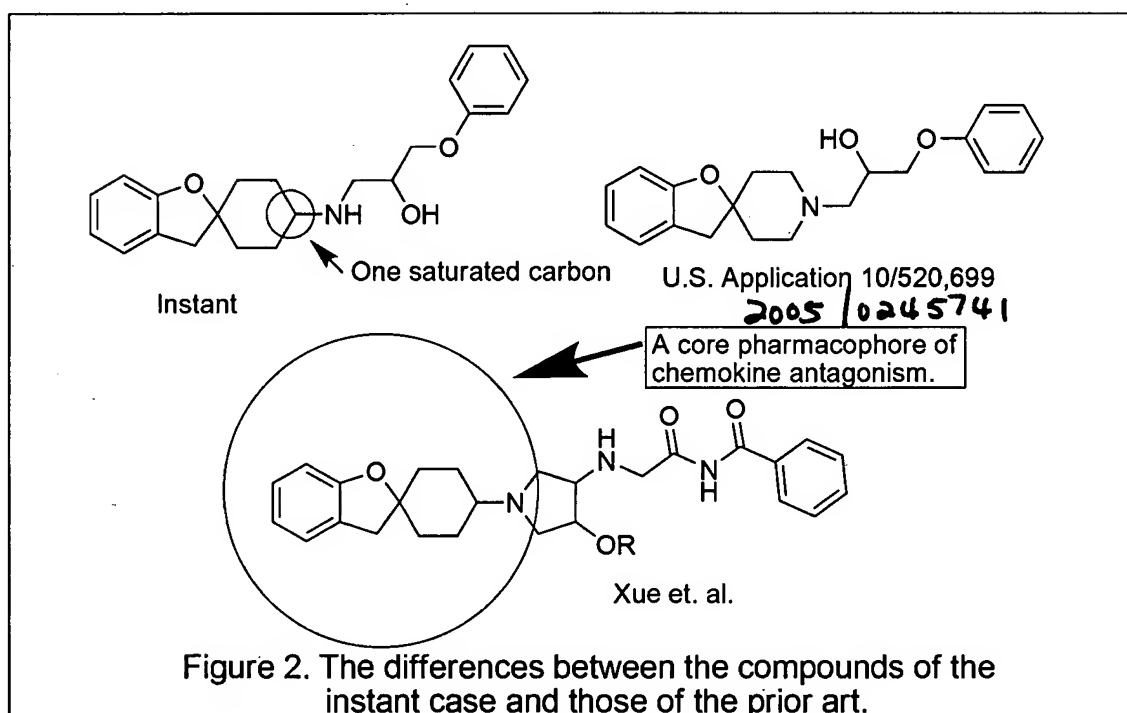


***Ascertainment of the difference between the prior art and the claims
(MPEP 2141.02)***

Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene group. By inserting a what is formally a methylene (CH_2 actually CH in the ring and H on N) into the compounds of Hossain, Nafizal; Ivanova, - Svetlana & Mensonides-Harsema, Marguerite a

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spiro[benzofuran-2,1'-cyclohexan]-4'-amine is produced, which is a core pharmacophore of chemokine antagonism. These relationships are illustrated graphically in Figure 2.



Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the

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teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis v. trans*) or position isomers (emphasis added) (e.g. *ortho v. para*)".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

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double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10 of copending Application No. 10/579,545 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here.

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12 of copending Application No. 10/581,171 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. This is a provisional obviousness-type double patenting rejection.

7. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, 14 of copending Application No. 10/583,468 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. Although claim 9 is apparently a claim for "a claim".

8. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13 of copending Application No. 10/520,699 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here.

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This is a provisional obviousness-type double patenting rejection.

9. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claim 1-7, 9, 11 of commonly assigned copending Application No. 11/744,659. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

10. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-7, 9, 11 of commonly assigned copending Application No. 11/744,677. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant

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application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

- (A) ***The breadth of the claims;***
- (B) ***The nature of the invention;***
- (C) ***The state of the prior art;***

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- (D) *The level of one of ordinary skill;*
- (E) *The level of predictability in the art;*
- (F) *The amount of direction provided by the inventor;*
- (G) *The existence of working examples; and*
- (H) *The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill:** One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually

looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).....” Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim IX Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

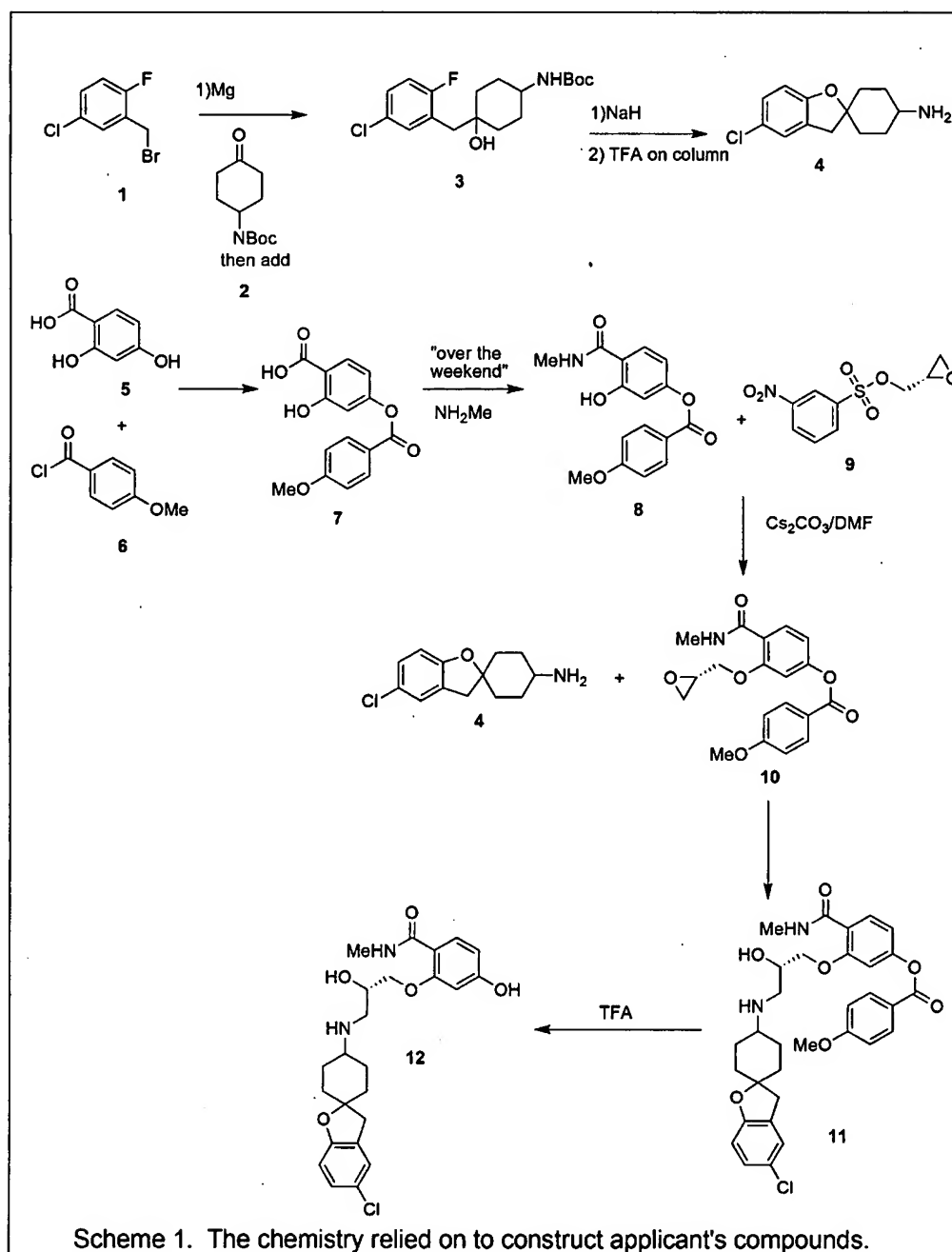
As per MPEP:

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily

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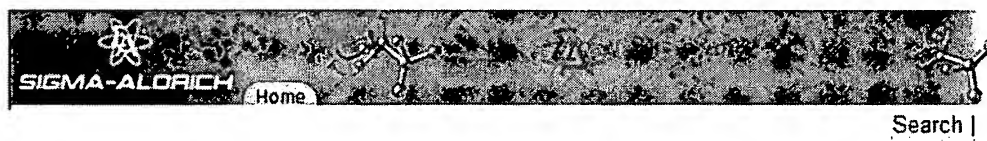
available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The synthetic route and starting materials that the applicant has provided to make the scope of this invention has been reproduced below as Scheme1:



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The key materials here are the α -bromo-2-fluoro-toluene derivative **1**, the N-Boc-4-amino cyclohexanone **2**, phenols such as **8** bearing amide groups, and glycidols **9**. A search for each of these materials in the Aldrich Chemical Company catalog (St. Louis, MO) was conducted, the results of which are reproduced below:



Enter Search Criteria

Search CLEAR

Search Type: SubStructure (2D)

Structure:

CLR NEW DEL D-R UDO JME

C N O S F Cl Br I X

JME Editor courtesy of Peter Ertl, Novartis

SMILES: Load

MW: Between &

Results / Page: 50

Total Hits: 2000

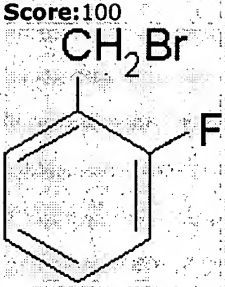


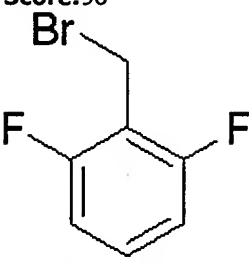




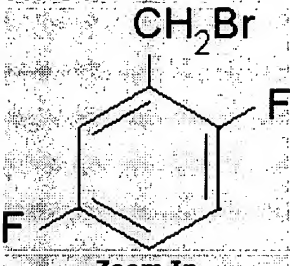


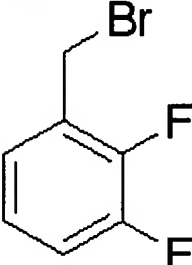






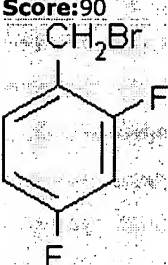


[More Options](#)

Search Results 1-15 of 15 in 0.0 sec.

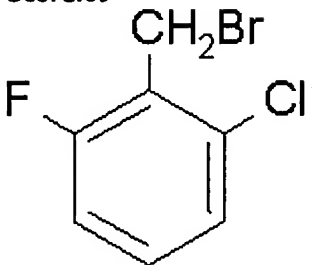

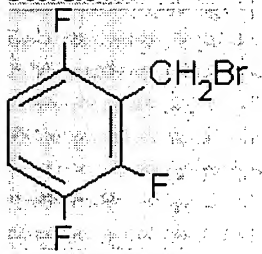

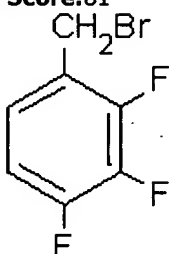

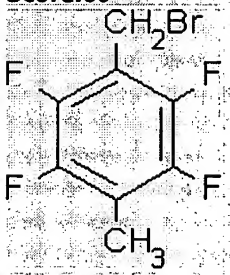

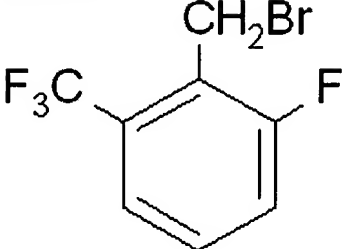

[New Search](#)[Export](#)

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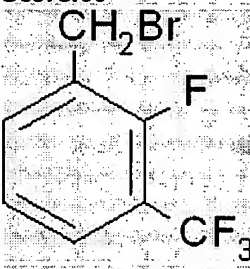

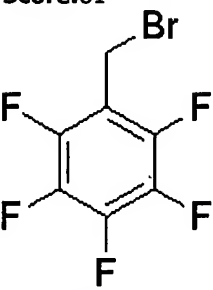



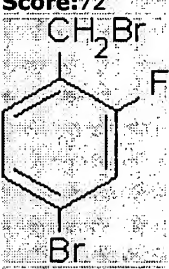

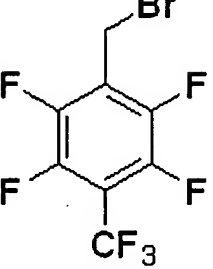


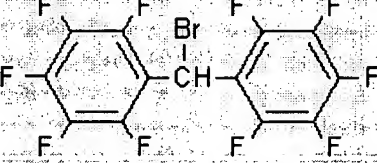
Sort By:

MW	Compound Properties	Structure	Add #	Prod. #	Purity
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	Name: 2,6-Difluorobenzyl bromide IUPAC: 2-(bromomethyl)-1,3-difluorobenzene MF: C ₇ H ₅ BrF ₂ CAS #: 85118-00-9 MW: 207.02 MDL #: MFCD00000329 FP: 230	Score:96  Zoom In	  83141 purum, ≥95.0% (GC)   264431 97%		
	Name: 2,5-Difluorobenzyl bromide IUPAC: 2-(bromomethyl)-1,4-difluorobenzene MF: C ₇ H ₅ BrF ₂ CAS #: 85117-99-3 MW: 207.02 MDL #: MFCD00009897 FP: 60 d: 1.6090	Score:84  Zoom In	  264423 98%		
	Name: 2,3-Difluorobenzyl bromide IUPAC: 1-(bromomethyl)-2,3-difluorobenzene MF: C ₇ H ₅ BrF ₂ CAS #: 113211-94-2 MW: 207.02 MDL #: MFCD00042488 FP: 194 d: 1.6280	Score:86  Zoom In	  68318 ≥99.5% (GC)   74259 purum, ≥99.5% (GC)   265314 98%		
	Name: 2,4-Difluorobenzyl bromide IUPAC: 1-(bromomethyl)-2,4-difluorobenzene MF: C ₇ H ₅ BrF ₂ CAS #: 23915-07-3 MW: 207.02 MDL #: MFCD00011649 FP: 104 d: 1.6130	Score:90  Zoom In	  264415 98%		

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Name: 2-Chloro-6-fluorobenzyl bromide IUPAC: 2-(bromomethyl)-1-chloro-3-fluorobenzene MF: C ₇ H ₅ BrClF CAS #: 68220-26-8 ► MW: 223.47 MDL #: MFCD00040126 FP: 230 d: 1.6290	Zoom In Score:69  Zoom In	 A 539090 96%
Name: 2,3,6-Trifluorobenzyl bromide IUPAC: 2-(bromomethyl)-1,3,4-trifluorobenzene MF: C ₇ H ₄ BrF ₃ CAS #: 151412-02-1 ► MW: 225.01 MDL #: MFCD00061208 BP: 114 °C FP: 195 d: 1.7180	Zoom In Score:84  Zoom In	 A 449407 97%
Name: 2,3,4-Trifluorobenzyl bromide IUPAC: 1-(bromomethyl)-2,3,4-trifluorobenzene MF: C ₇ H ₄ BrF ₃ CAS #: 157911-55-2 ► MW: 225.01 MDL #: MFCD00061233 FP: 195 d: 1.71	Zoom In Score:81  Zoom In	 A 554685 97%
Name: 1-Bromomethyl-4-methyl-2,3,5,6-tetrafluorobenzene IUPAC: 1-(bromomethyl)-2,3,5,6-tetrafluoro-4-methylbenzene MF: C ₈ H ₅ BrF ₄ CAS #: 92814-00-1 ► MW: 257.02 MDL #: MFCD03001155 FP: 199	Zoom In Score:80  Zoom In	 A 556491 97%
Name: 2-Fluoro-6-(trifluoromethyl)benzyl bromide IUPAC: 2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene MF: C ₈ H ₅ BrF ₄ CAS #: 239087-08-2 ► MW: 257.02 MDL #: MFCD00082477 FP: 225	Zoom In Score:67  Zoom In	 A 539627 98%


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Name: 2-Fluoro-3-(trifluoromethyl)benzyl bromide IUPAC: 1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene MF: C ₈ H ₅ BrF ₄ CAS #: 184970-25-0 MW: 257.02 MDL #: MFCD00061172	Score: 66 	 A <u>538094</u> 97%
Name: 2,3,4,5,6-Pentafluorobenzyl bromide IUPAC: 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene MF: C ₇ H ₂ BrF ₅ CAS #: 1765-40-8 MW: 260.99 MDL #: MFCD00000299 BP: 174 - 175 °C FP: 181 d: 1.7280	Score: 81 	 17910 puriss., ≥99.0% (GC)  A <u>101052</u> 99%  S <u>33001</u> ampule of 5 g
Name: 4-Bromo-2-fluorobenzyl bromide IUPAC: 4-bromo-1-(bromomethyl)-2-fluorobenzene MF: C ₇ H ₅ Br ₂ F CAS #: 76283-09-5 MW: 267.92 MDL #: MFCD00055467	Score: 72 	 A <u>477559</u> 98%
Name: 2,3,5,6-Tetrafluoro-4-(trifluoromethyl)benzyl bromide IUPAC: 1-(bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene MF: C ₈ H ₂ BrF ₇ CAS #: 76437-40-6 MW: 310.99 MDL #: MFCD00191855 FP: 210 d: 1.8640	Score: 60 	 87285 purum, ≥97.0% (GC)  A <u>406406</u> 98%
Name: DECAFLUOROBENZHYDRYL BROMIDE IUPAC: DECAFLUOROBENZHYDRYL BROMIDE MF: C ₁₃ HBrF ₁₀ CAS #: 5736-4-9--2 MW: 427.04 MDL #: MFCD00017901	Score: 51 	

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Most disturbingly we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made. We can see that R_1 can be nothing but fluoro, trifluormethyl or chloro.

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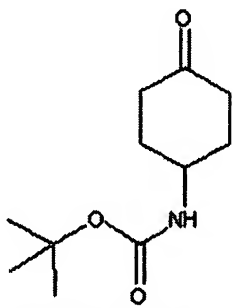
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No such cyclohexanones appear to be commercially available. While many phenols such as **8** are commercial, it would appear that the amide functionality (reverse as well) is required for activity, based on the fact that applicant has no examples of compounds that are not amides (in the ortho position) and the fact that Xue et. al. (supra) require the amide moiety for antagonism. To the examiners knowledge only one nosylglycidol, namely compound **9**, is commercial. Substituents should be limited to lower alkyl.

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed*, (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required starting materials of formula **1**, **2**, **8**, and **9** are to be obtained. Where may the directions to prepare or buy them be found?

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In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). *Genetech Inc Vs Nova Nordisk* 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the

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less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

If such starting materials could be obtained compounds could be obtained it is very

clear that the protracted list of substituents for R¹ cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by

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Grignards (Jie Jack Li *Name Reactions A Collection of Detailed Reaction Mechanisms* "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur (Knochel et. al. *Angew. Chem. Int. Ed.* **2003**, 42, 4302 –4320). The "alkylhalo" compounds will undergo metal halogen exchange when in the presence of a Grignard (Knochel *ibid.*).

Another disturbing feature of what is before the examiner, is the fact that it appears that no assays were performed. These compounds may perform in this assay however this has not been asserted. There is no support in the specification for the use of these compounds as chemokine antagonists. While applicant states on pg. 40 "Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of M1P-1 α chemokine." No evidence is given that these compounds actually were shown to have this activity. Given that similar compounds have the activity we can assume they have this activity (*supra*). The assumption that a chemokine receptor is involved may be incorrect, given that agonism at other GPCRs (δ -opioid receptors for instance), can lead to down regulation of chemokine receptors via heterodimers or higher oligomer complex formation (Chen et. al. *European Journal of Pharmacology* **2004**, 483, 175-186.). The complete receptor profile of THP-1 cells is not known. Applicant may consider a binding assay as in Carroll et. al. WO 00/014086 cited by applicant ref. AG pg. 34:

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plate counts.

- The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I -RANTES or ^{125}I -MIP-1 α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ^{125}I -MIP-1 α .

or Bondinell et. al. WO 01/64213 A1 pg. 23-25 cited by applicant ref. AH

25 Biological Data:

CCR5 Receptor Binding Assay

- CHO cell membranes (0.25×10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with $0.3 \text{ }^{125}I$ -RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 μ l). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3 . The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

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CCR5 Receptor Functional Assay

- The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 or mCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by
- 5 Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2×10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM
- 10 NaHCO_3 , 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM CaCl_2 , 1 mM MgCl_2 and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2×10^6 cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at
- 15 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM CaCl_2 , 1 mM MgCl_2 and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer
- 20 (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+}
- 25 attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50} , defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of
- 30 antagonists). Alternatively, this CCR5 receptor functional assay was performed on murine CCR5 (mCCR5) with a RANTES concentration of 2nM.

- The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 μM . The full structure/activity relationship has not yet been established for the compounds of this invention.
- 35 However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators

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The following is a quotation of the second paragraph of 35 U.S.C. 112:


The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 9 recite the limitation "solvate" in the claim. There is insufficient antecedent basis for this limitation in the claim.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, Ph.D. whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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